M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DATE: Feb 2, 2005

FROM: Dianne Murphy, MD
Director
Office of Pediatric Therapeutics
Office of the Commissioner

SUBJECT: Overview of the February 14, 2005 Meeting of the Pediatric Advisory Committee (PAC)

TO: Members of the Pediatric Advisory Committee

The focus of the February 14th 2005 Pediatric Advisory Committee (PAC) meeting will be safety. We will begin with a discussion of adverse event reports for 6 drugs granted pediatric marketing exclusivity. Following the adverse event reports, the committee will discuss and provide input on options for improving pediatric post-marketing drug adverse event monitoring as mandated by the Best Pharmaceutical Act for Children (BPCA). The meeting will begin at 2:00 PM and end at 6:00 PM. A draft agenda for the meeting follows this memorandum.

After brief introductions, Medical Officers within the Center of Drug Evaluation and Research's Division of Pediatric Drug Development will report on adverse events for the first year of marketing following the granting of exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act for the following 6 drugs: LOTENSIN® (benazepril), BREVIBLOC® (esmolol), XENICAL® (orlistat), GLUCOVANCE® (glyburide/metformin), MALARONE® (atovaquone/proguanil), and VIRACEPT® (nelfinavir). These reports are required under section 17 of the BPCA. This will bring to 34 the number of products whose 1-year post-pediatric market exclusivity adverse events have been reviewed and reported to the PAC and it predecessor.

Following the adverse event reports, Dr. Solomon Iyasu will present a summary of the feedback from committee members received by the Office of Pediatric Therapeutics (OPT) regarding the format and advent event information presented to the pediatric advisory committee. Dr. Iyasu will also present options regarding the content and presentation format of the BPCA-mandated safety reviews and options for enhancing pediatric post marketing adverse event monitoring for discussion by the committee. The committee will also be asked to specifically address the following questions.

Question 1: OPT proposes to submit an abbreviated written summary report to the PAC for drugs where the 1-year safety review does not raise a safety concern i.e. there were no post-marketing

reports submitted or the reported pediatric events did not provide any concern of a possible safety risk. The entire written summary will not be presented at a public PAC meeting. However, a slide summarizing the products reviewed and our recommendation to the PAC will be presented. The PAC will still retain the opportunity to comment upon our recommendation at a public hearing. Do you concur with this approach?

Question 2: OPT proposes to provide a public presentation of the mandated safety review at the PAC meeting for drugs where the 1-year safety review raised a possible pediatric safety signal i.e. increase in the frequency or severity of expected adverse events relative to adults or background rate; occurrence of unexpected or new serous pediatric events; reports of events that are unique to pediatric patients. When possible, in addition to the adverse event reporting and our usual review, the presentation will include an assessment of incidence rates, biological plausibility and review of the literature. Do you concur with this approach?

Question 3: The limitations of spontaneous post-marketing adverse event reporting system are well known to you. Please discuss and prioritize potential programs, assuming additional resources were available, to supplement and/or overcome the limitations of spontaneous reporting system for assessing and monitoring safety of marketed drug products in the pediatric populations. Some examples of potential programs include:

a. Population-based active surveillance
b. Analysis of claims databases (e.g. United Health Group, Harvard Pilgrim, TenCare)
c. Exposure and/or outcome/disease registries and creation of linkages with AERS
d. Long-term pediatric safety studies to assess drug adverse events including assessment of growth and development; discuss if and how prioritization of products for additional long-term studies might be approached.

The background package for the adverse event review portion of the February 14th meeting includes the following documents under separate tabs for each drug in addition to this cover memo:

- Draft of the slide presentations for the 6 products.
- 1-year Post-Pediatric Exclusivity Post-marketing Adverse Event Reviews for all 6 drugs granted exclusivity
- 1-year Post-Pediatric Exclusivity Drug Use Reviews for all 6 drugs granted exclusivity
- Summary of the Clinical and Pharmacology/Toxicology reviews of trials conducted for pediatric exclusivity for these 6 drugs
- Product labeling for all 6 drugs to be presented during the adverse event reporting portion of the meeting (please note that there is an indication in the margin of each label that identifies the pediatric sections of the product label)

The FDA relies on the knowledge, judgment, experience and wisdom of scientists and practitioners like you to help address safety of medications in the pediatric population. We thank you for your time and effort, and we look forward to seeing you and hearing from you on Feb 14th.